UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/025,195	12/19/2001	David Berd	1225/1D414US2	8483

7590 09/03/2003

DARBY & DARBY P.C.
805 Third Avenue
New York, NY 10022

EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 09/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/025,195	Berd
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 8, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above, claim(s) *3 and 9-21* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, and 4-8* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *3, 9*
4) ☒ Interview Summary (PTO-413) Paper No(s). *10*
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Election filed July 8, 2003 (Paper No. 8) in response to the Office Action of April 9, 2003 (Paper No. 6) is acknowledged and has been entered. Claims 1-21 are pending in the application and Claims 3, 8-21 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1, 2 and 4-8 are currently under prosecution.

2. Applicant's election of Group I, claims 1, 2, 4-8 for examination without traverse is acknowledged. It is noted that Applicant inadvertently neglected to respond to the requirement for election of species in Paper No. 6, Section 6, page 12. In the interests of compact prosecution, Examiner called Dr. Anna Lovqvist and requested a telephone election of the species requirement. Dr. Lovqvist elected the species of dinitrophenyl (See Telephone Interview, Paper No. 10). Affirmation of this election must be made by applicant in responding to this Office action.

3. Upon review and reconsideration it was found that Group I is further subject to election of species.

Claim 1 is generic to a plurality of disclosed patentably distinct species comprising adenocarcinomas with different pathogenesis and etiologies wherein the adenocarcinomas are (a) ovarian carcinoma and (b) colon carcinoma, both of claim 2.

A telephone call was made to Anna Lovqvist, (212) 527-7700 on August 26, 2003 to request an oral election to the above restriction requirement

Dr. Lovqvist made an oral election to the above restriction requirement, and elected the species of colon carcinoma (See Telephone Interview, Paper No. 10).

Affirmation of this election must be made by Applicant in responding to this Office action.

Specification

4. The specification on page 1 should be amended to reflect the status of the parent applications. Appropriate correction is required.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1, 2, 4-8 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of US

Patent No. 6,333,028. Although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept. The instant claims are generic to the patented claims and would have been obvious in view of the patented claims which have all of the characteristics of a method of treating an adenocarcinoma, wherein the tumor cells are autologous, wherein the hapten is DNP, wherein the composition is mixed with an immunological adjuvant, wherein the immunological adjuvant is Bacille Calmette-Guerin.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claim Rejections - 35 USC § 112

8. Claims 1,2, 4-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating adenocarcinoma/colon carcinoma comprising administering autologous irradiated colon carcinoma cells from the colon carcinoma of a patient to the patient, does not reasonably provide enablement for administering syngeneic human tumor cells substantially in a no growth phase. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a method for treating adenocarcinoma/colon carcinoma comprising administering syngeneic human tumor cells substantially in a no growth phase. This includes tumor cells that still are able to grow and divide.

As drawn to the syngeneic human tumor cells, the specification teaches that the compositions of the present invention include a composition prepared from a tumor cell which is hapten modified and syngeneic to the type of tumor to be treated (abstract). Class I MHC-restricted T cell clones generated from mice immunized with TNP-modified syngeneic lymphocytes respond to MHC-associated TNP-modified "self peptides" (col 2, lines11-14). Tumor cells for use in the compositions of the invention are preferably syngeneic, i.e. autologous, to the cancer which is to be treated. For the purposes of the present invention, syngeneic refers to tumor cells that are genetically identical (co 7, lines 9-15). One cannot extrapolate the teaching of the specification to the scope of the claims because no syngeneic human cells other than autologous cells have been taught. Although the specification refers to mice immunized with TNP-modified syngeneic lymphocytes, Examiner takes note that strains of laboratory mice are inbred for a great number of generations and therefore become syngeneic. The same is clearly not true of humans. Other than autologous cells, the specification provides no information on a source of syngeneic cells. The specification provides insufficient guidance with regard to this issue and provides no working examples which would provide guidance to one skilled in the art as to sources of human syngeneic cells other than

autologous tumor cells. For the above reasons, it appears that undue experimentation would be required to make the broadly claimed syngeneic cells used in the invention.

As drawn to the cells substantially in a no growth phase, the specification teaches that the tumor cells of the present invention may be live, attenuated or killed cells. Tumor cells which are not going to grow and divide after administration are preferred for use in the present invention. Conventional methods of suspending cells in a state of no growth are known to the skilled artisan. Tumor cells may be irradiated prior to use such that they do not grow (p. 10, lines 15-25). One cannot extrapolate the teaching of the specification to the scope of the claims because it is clear that as written, the claims read on cells which are still able to grow and divide. That is, the claims read on haptenized tumor cells, some of which are in a non growth phase and also reads on haptenized tumor cells which are going into or leaving a no growth phase, such as entering or progressing from GO phase. There is no definition in the specification that details what the term "substantially" in a no growth phase means. It is clear that use of the cells, as claimed, in the treatment of a human patient would be expected to result in exacerbation of, rather than a treatment of the disease. Further, although the specification teaches that conventional methods of suspending the cells in a state of no growth are known to the skilled artisan, the specification does not teach, other than conventional irradiation, how to produce haptenized tumor cells that will maintain a no growth phase (i.e. those in G0 phase) and it could not be predicted from the information in the specification what other method could be used to permanently maintain a no

growth phase or when or whether the haptenized cells, suspended by any other method, would return to a "growth phase". The method as claimed would be expected exacerbate rather than mitigate the tumor by administering cells that would be expected to form additional metastases. In view of the above, one of skill in he art would be forced into undue experimentation to practice the claimed invention.

9. If Applicant were able to overcome the rejection under 35 USC 112, first paragraph above, claims 1, 2, 4-7 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating an adenocarcinoma/colon cancer in a human patient comprising administering the haptenized syngeneic colon cancer cells and BCG, does not reasonably provide enablement for treatment an adenocarcinoma/colon cancer in a human patient without administering BCG in combination with the claimed composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to treatment of adenocarcinoma/colon cancer with a composition comprising a hapten conjugated to a syngeneic colon cancer cell.. The specification teaches a colon cancer vaccine administered with BCG (p 42, lines 1-4). One cannot extrapolate the teaching of the specification to the scope of the claims because both US Patent No. 5,290,551(IDS item) and Hoover et al (Cancer, 1985, 55:1236-1243) specifically teach the successful administration of anti-cancer vaccines with BCG. Further, Hoover et al, *Supra* states that the correct amount of the appropriate adjuvant was a critical condition of the success of the

immunotherapy using irradiated autologous colon tumor cells (p. 1242, col 1, para 2). It appears that the inclusion of the BCG adjuvant may be a critical step since Livingston et al., (Can. Res. 1989, 49:7045-7050) disclosed that in a melanoma vaccine using the GM2 ganglioside, antibody responses were not induced unless BCG was added to the purified GM2 vaccine (p. 2913, paragraph bridging columns 1 and 2). Livingstone et al also state that "adjuvants ..... were important factors in the mouse studies and results of the present human trials indicate their importance in melanoma patients". Based on the teachings above and in the specification one of skill in the art would not expect that the claimed method would be effective in treating adenocarcinoma/colon cancer with DNP-conjugated vaccines without specifically including BCG as disclosed in the specification. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

10. Claims 1, 2 and 4-8 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2 and 4-8 are indefinite in the recitation of the phrase "tumor cell substantially in a no growth phase" in claim 1. The claims are confusing because the metes and bounds of the claims cannot be determined because it is unclear, for example, whether the claims are drawn to tumor cells that are proceeding into or just out of GO phase or whether the claims are drawn to tumor cells, some of which are in a no growth phase and some of which are not. Further, substantially as drawn to a "no growth phase" is not defined by the specification and thus it is a relative

term. The specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

12. Claims 1, 2, 4-8 are rejected under 35 USC 103(a) as being unpatentable over Hoover et al (Cancer, 1985, 55:1236-1243) in view of US Patent No. 5,290,551.

The claims are drawn to a method for treating adenocarcinoma/colon carcinoma comprising administering hapten modified syngeneic/autologous human tumor cells substantially in a no growth phase and an adjuvant, wherein said human suffers from a malignant tumor of the same type as the tumor cell, wherein the tumor is colon carcinoma, wherein the tumor cells are autologous, wherein the hapten is

DNP, wherein the composition is mixed with an immunological adjuvant prior to administration, wherein the immunological adjuvant is Bacille Calmette-Guerin (BCG).

Hoover et al teach a successful method of active-specific immunotherapy of human colon cancer with an irradiated (p. 1238, col 2, para 2) syngeneic human colon tumor cell/bacillus calmette-Guerin vaccine (abstract and table 1, p. 1240) wherein the method produced significant improvement in both disease-free status and survival of the immunized patients when compared to unimmunized controls (see Figure 2, p. 1240 and col 2, p.1240). Hoover et al teach as set forth but do not teach a method wherein the irradiated human colon tumor cells are haptenized with DNP.

US Patent No. 5,290,551 teaches a method of treatment of cancer patients/human melanoma patients with irradiated DNP haptenized autologous human melanoma cells (see abstract) mixed with BCG (see claim 2). Most tumor immunologists agree that getting T lymphocytes into the tumor mass is a prerequisite for tumor destruction by the immune system (col 2, lines 44-48). The efficiency of the instant vaccine process for the treatment of cancer has been increased by immunizing with tumor cells conjugated to DNP (col 3, lines 12-15), wherein infiltration of T lymphocytes into the tumor mass is observed. This approach, which increases the number and capacity of lymphocytes entering the tumor is a significant advance in the art (para bridging cols 3 and 4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to haptenize the syngeneic human colon tumor cells

of Hoover et al with DNP using the method of method of US Patent No. 5,290,551 for the treatment of colon cancer because Hoover et al teach a successful method of active-specific immunotherapy of human colon cancer with an irradiated syngeneic human colon tumor cell/bacillus calmette-Guerin vaccine and because US Patent No. 5,290,551 specifically teaches that haptenization with DNP increases the efficiency of the vaccine process wherein infiltration of T lymphocytes into the tumor mass is observed and this approach, which increases the number and capacity of lymphocytes entering the tumor, is a significant advance in the art. One would have been motivated to haptenize the syngeneic human colon tumor cells of Hoover et al with DNP, using the method of method of US Patent No. 5,290,551, for the treatment of colon cancer because US Patent No. 5,290,551 specifically teaches that most tumor immunologists agree that getting T lymphocytes into the tumor mass is a prerequisite for tumor destruction by the immune system and further teaches that the haptenization approach, which increases the number and capacity of lymphocytes entering the tumor, is a significant advance in the art. Given that the method of Hoover et al successfully treated colon cancer, given the teaching that most tumor immunologists agree that getting T lymphocytes into the tumor mass is a prerequisite for tumor destruction by the immune system, given the teaching that the haptinization approach increases the number and capacity of lymphocytes entering the tumor, one would have a reasonable expectation of success of treating colon carcinoma with the method of the combined references.

13. No claims allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
August 26, 2003